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EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
03/03/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/628,554	COMINGS ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7 and 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 2, 3, 5, and 6 are cancelled
Claims 1, 4, 7, and 8 are pending.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/11/2007 has been entered.

This Office Action is in reply to Applicants' correspondence of 4/11/2007.
Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.
This Action is **NON-FINAL**.

New Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

1. Claims 1, 4, 7, and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4, 7, and 8 are unclear over recitation of the phrase 'the DNA of the sample', as recited in part b) of claim 1. There is not proper antecedent basis for any 'DNA of the sample' in the claims. See MPEP 2173.05(e). The claims may be made more clear if part a) of claim 1 is amended to indicate that the sample obtained from the human subject contains DNA.

Maintained Claim Rejections - 35 USC § 112 1st – Description, New Matter

2. Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 8 requires a comparison of the time of survival between a human subject who is homozygous for the CCR5 delta 32 mutation as compared with a subject who is heterozygous for the CCR5 delta 32 mutation. However, the specification does not teach any such comparison. The specification provides only for the comparison of subjects homozygous or heterozygous for the deletion versus subjects homozygous for lack or the deletion mutation. For example, the comparison on page 7 of the instant specification teaches the death hazard ratio of the CCR5 12 + 22 versus the 11 genotype, and Fig 2 shows survival curves separated by CCR5 11 vs. 12 or 22 genotypes (where in each case the 2 allele is the deletion mutation). While Table 1

(page 10) presents data regarding one subject with a 22 genotype, the table does not teach any particular comparison between subjects with the 12 versus the 22 genotype.

Additionally, the specification does not appear to provide basis for the concept of predicting that a subject's survival time will be shorter if the subject has a homozygous CCR5 delta 32 deletion as compared to a subject heterozygous for the deletion mutation.

Response to Remarks

Applicants Remarks of 04/16/2207 have been fully and carefully considered. Applicants have traversed the rejection of claim 8 under 35 USC 112 1st ¶ as new matter. Applicants assert that from the presentation of data in the specification at pages 7-10, one of ordinary skill in the art would recognize that a subject homozygous for the CCR5 delta 32 mutation would be expected to have a shorter survival time than a heterozygous subject. The examiner maintains that while the specification presents a table of data points from heterozygous individuals, homozygous-wild type individuals and homozygous-deletion individuals, the specification provides only for comparisons wherein heterozygous and homozygous-deletion individuals taken together as a combined population. There is no teaching or contemplation of an additive effect of the mutation in a homozygous-deletion versus a heterozygous individual. The analysis of the data (specifically on p.7) with regard to the comparison of subjects with the 11 genotype (i.e. homozygous for the normal allele) to heterozygous subjects (i.e. with the 12 genotype), is not a comparison of subjects with the 12 genotype to subjects with the 22 genotype.

The rejection as set forth is **MAINTAINED.**

Maintained Claim Rejections - 35 USC § 112 1st ¶ – Scope of Enablement

3. Claims 1, 4, and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> A method for predicting the relative survival time of a human subject having multiple sclerosis (MS) comprising:
> a) obtaining a sample comprising DNA from a human subject having multiple sclerosis; and
> b) detecting in said DNA the presence or absence of a CCR5 delta 32 mutation, wherein the presence of a CCR5 delta 32 mutation in a subject with MS is predictive of a reduced time of survival as compared to a subject having MS and not possessing a CCR5 delta 32 mutation.

does not reasonably provide enablement for the correlation of the presence of the delta 32 mutation with increased relative survival of a human MS patient, or any comparison of human subjects that are homozygous for the delta 32 mutation versus subjects heterozygous for the delta 32 mutation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The claims are drawn to a method for determining the survival time of a subject with MS. The method comprises detecting the presence of a mutation in the CCR5 gene, wherein the mutation correlates to reduced time of survival in subjects having MS.

Claims 1 and 4 encompass the detection of a CCR5 delta 32 mutation wherein the presence or absence of the mutation may correlate with either an increase or decrease in relative survival time, thus the claims encompass a method in which

presence of the delta 32 CCR5 mutation correlates with an increased relative survival time in a patient with MS.

Claim 8 is drawn to a method for the comparison of relative survival time between an MS subject homozygous for the delta 32 deletion mutation and a subject heterozygous for the delta 32 mutation.

The nature of the invention requires knowledge of a correlation between the delta 32 CCR5 gene mutation and the relative survival time of a subject having MS.

Direction provided by the specification and working examples

The specification teaches an example of the analysis of the CCR5 delta 32 mutation in DNA isolated from post-mortem human brain tissue from 132 MS cases (p.6). The specification teaches that survival analyses were used to test the effect of the CCR5 delta 32 deletion survival (p.7). The specification teaches that there is a significant association between the CCR5 delta 32 deletion allele (allele 2) with early death. When the subject genotypes were analyzed according to placement into one of five groups based on years of survival after disease onset (≤5 yrs, 6-10 yrs, 11-15 yrs, 15-20 yrs, and ≥21 yrs), subjects lacking a copy of the CCR5 delta 32 deletion allele survived progressively more years as compared to subjects possessing at least one copy of the delta 32 deletion mutation allele of the CCR5 gene (p.7; p.10 Table 1). The specification teaches that the analysis reveals that MS patients with at least one copy of the delta 32 CCR5 allele (the 12 and 22 genotypes) have over twice the mortality as compared to the 11 genotype (subjects not having a copy of the delta 32 CCR5 deletion mutation).

The specification does not provide any comparative analysis other than subject groups without the delta 32 mutation (i.e. the 11 genotype) and a combined group of mutation carriers (i.e. the 12 and 22 genotypes together as a single group).

The specification does not offer any external validation of the alleged correlation between the CCR5 delta 32 mutation and survival time. The specification does not teach the successful application of the methods to any population other than those in which the asserted correlation was established. It is therefore unknown if the CCR5 delta 32 deletion mutation would be predictive of relative survival time in MS patients in any other population.

State of the art, level of skill in the art, and level of unpredictability

While the level of skill in the art of identifying genetic mutations is quite high, there is a high level of unpredictability with regard to any given mutation being associated with a particular phenotype or disease course, as well as the assumption of homozygous versus heterozygous effects where such effects have not been established. Additionally, the prior art indicates the unpredictability in using the CCR5 delta 32 deletion mutation as an indicator of relative survival time in subjects with MS.

There is a large body of knowledge in the prior art related to mutations and polymorphisms in general, and their association with specific phenotypes including disease states. However, the art is highly unpredictable with regard to the functionality of a given genomic mutation. After a mutation is identified, it is unpredictable whether any such mutation would be associated with any phenotypic trait such as a disease state in every population. For example, Hacker et al teaches that they were unable to

confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627).

The prior art specific to the CCR5 delta 32 deletion mutation and relative time of survival also indicates the unpredictability of using the presence of the CCR5 delta 32 deletion as an indicator of a shorter relative time of survival. Sellebjerg et al (2000) (as cited in the IDS) teaches an analysis of the CCR5 delta 32 mutation as it correlates to several parameters of disease course in subjects with MS. Sellebjerg et al teaches that the age of onset of disease is lower in patients carrying the delta 32 deletion mutation of the CCR5 gene than in the remaining patients (p.100 – Results *3.1 CCR5 Δ32 in patients and control subjects*). Midgard et al (1995) (as cited in the IDS) teaches an analysis of several prognostic factors for survival time in MS. Midgard et al teaches that the shortest survival is in patients with a high age at onset (p.418 – Results; Table 1). Taken together, these references would indicate that the delta 32 deletion mutation of the CCR5 gene is indicative of a longer relative survival time.

Because the claims encompass the comparison of homozygous versus heterozygous delta 32 mutation carriers, it is relevant to point out that the specification provides no analysis of a comparison between such subject populations. The specification teaches that of the 132 subjects of the study, only one subject was homozygous for the delta 32 mutation. Thus, while the instant specification teaches the analysis of delta 32 mutation carriers (i.e. the combined 12 and 22 group) versus non-carriers (i.e. the 11 genotype group), the specification does not establish whether or not

there is any significant difference between homozygous versus heterozygous delta 32 carriers (i.e. the 12 versus the 22 genotype).

Quantity of experimentation required

A large and prohibitive amount of experimentation would have to be performed in order to make and use the invention in the full scope of the claims. Such experimentation would include establishing a predictive relationship in which presence of the delta 32 mutation correlates with an increased relative survival time. Such experimentation would also require a comparative analysis of a statistically relevant sample size of homozygous deletion mutation carriers as compared to heterozygous deletion mutation carriers to establish a statistically significant difference between relative survival time of MS subjects in the two groups.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and the breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the amount of guidance by the applicant and the paucity of working examples, it is the conclusion the an undue amount of experimentation would be required to make and use the invention in the full scope of the claims.

Response to Remarks

Applicants have traversed the rejection of claims 1, 4, and 8 under 35 USC 112 1st ¶ for lacking full enablement. Applicants have argued (p.4 of Remarks), with respect to the subject matter of claim 8, that the artisan of ordinary skill would understand that a

subject who is homozygous for the CCR5 delta 32 mutation would be expected to have a shorter survival time than a subject who is heterozygous for the deletion. The argument, which does not address the breadth of claims 1 and 4 as rejected above, has been considered but is not found to be persuasive. There is no evidence of the causality or mechanism for any effect of the CCR5 delta 32 deletion mutation and survival time with MS. As such the specification does not indicate that there is any reliably determined and significant difference in the survival of a heterozygous versus a homozygous-deletion individual. The specification does not teach if the mutation is for example, a dominant negative mutation, where the inclusion of an additional mutant allele in the homozygous individual will not further affect the phenotype seen in the heterozygous individual. Applicants' traversal of the rejection of claims under 35 USC 112 1st¶ for lack of enablement has been addressed in the Office Action of 10/11/2006. Applicant has not provided any evidence in the instant specification which, in view of the unpredictability of the method as demonstrated by the cited prior art, provides for a method that is reliable for the prediction of survival time with MS in the breadth of the methods as claimed.

Claim Rejections - 35 USC § 103

4. Claims 1 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barcellos et al (2000) (as cited in the IDS) in view of Midgard et al (1995) (as cited in the IDS).

Barcellos et al teaches the analysis of the CCR5 gene in a population of 125 families with multiple case of MS including 322 affected individuals (p. 283 - Results). The reference teaches obtaining samples from the individuals (white blood cells transformed into lymphoblastoid cell lines) (p.282 – *Genotyping*). Barcellos et al teaches that age of onset was approximately 3 years later in patients carrying the CCR5 delta 32 deletion (p.281 – Abstract; p.284 – Table 3).

Barcellos et al does not specifically teach that the CCR5 delta 32 deletion correlates to a reduced survival time in subjects having MS versus subjects having MS who do not posses the CCR5 delta 32 deletion.

Midgard et al teaches an analysis of several prognostic factors for survival time in MS. Midgard et al teaches that the shortest survival is in patients with a high age at onset (p.418 – Results; Table 1).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have combined the method and results of Barcellos et al with the teachings of Midgard et al to reach the conclusion that the presence of the CCR5 delta 32 deletion mutation in a subject with MS is predictive of a shorter survival time versus a subject that does not possess the CCR5 delta 32 deletion mutation. One would have been motivated to combine these methods and results in order to expand the amount of information provided by analysis of the CCR5 gene in subjects with MS. One would have had a reasonable expectation of success because both Barcellos et al and Midgard et al utilized populations of subjects with MS.

5. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barcellos et al (2000) in view of Midgard et al (1995) as applied to claims 1-3 above, and further in view of Cohen et al (2001) US Patent 6,265,546.

The teachings of Barcellos et al in view of Midgard et al are applied to claims 4-6 as they were previously applied to claims 1 and 7.

Barcellos in view of Midgard does not teach the use of whole blood to obtain a sample for genetic analysis.

Cohen et al teaches methods for the genetic analysis of disease related genes. Cohen teaches sources for obtaining DNA for genotyping analysis. Specifically, Cohen teaches that whole blood is a useful source of DNA for genotyping analysis, and recommends peripheral venous blood as a preferred source of genomic DNA for genotyping (col. 96 lns.10-33).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the methods of Barcellos et al in view of Midgard et al to have used DNA from whole blood as taught by Cohen et al. One would have been motivated to do so in order have an additional source of genetic material for the analysis of the CCR5 gene in subjects with MS. One would have had a reasonable expectation of success because Cohen et al teaches that the DNA from whole blood is suitable for genotyping analysis.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 103 as obvious in light of the teachings of Barcellos et al in view of Midgard et al. Applicants continue to argue (p.5-7 of the Remarks) that the Examiner's analysis of the references applied to the rejection of claims as obvious is flawed. Applicant argues that the presence of the delta 32 mutation correlated with shorter survival time cannot be supported unless the link between the presence of the mutation in an MS patient at a late age of onset of the disease is established in the art (Applicants remarks page 6, last ¶). The examiner maintains that the Barcellos et al reference applied in the rejection of claims under 35 USC 103 clearly teaches the association of the presence of the mutation and age of onset of MS. While applicant points out that in the rejection of claims for lack of enablement the Examiner indicates that a different reference (Sellebjerg et al) appears to provide teachings contradictory to Barcellos et al, it is relevant to point out that Sellebjerg et al is not in fact relied upon for the rejection of claims under 35 USC 103. Additionally, the references use different populations for study and Sellebjerg points out that the age of onset difference was only significant when the analysis was restricted to patients with intrathecal synthesis of oligoclonal bands (p.100 – CCR5 delta 32 in patients and control subjects) whereas the claims have no limitations regarding subject population). Thus while some prior art may lead to a different conclusion in a different particular subject sub-population, given the breadth of the claims and the teaching of the art relied upon, the examiner maintains that the teachings in the art can lead one of ordinary skill in the are to predict relative survival time based on the presence of the

CCR5 delta 32 mutation. Furthermore it is noted that, as currently written, claims 1 and 4 do not require a particular relationship between presence of the delta 32 mutation and relative survival time.

And while Applicant points out that ¶[0009] of the instant specification notes the seemingly inconsistent findings regarding the delta 32 mutation and MS age of onset (Remarks p. 7), it is relevant to point out that the post-filing art of Gade-Andavolu et al (2004) also teaches (p.127, right col., second paragraph in Results) that MS patients carrying the CCR5 normal allele had an earlier age at onset (thus subjects with the delta 32 allele have a later age of onset, in agreement with the teachings of Barcellos et al).

Applicant has not provided a convincing argument or any evidence as to why the cited references of Barcellos et al and Midgard et al do not render obvious a method in which CCR5 mutation is predictive of survival rate with MS. The Examiner maintains that the methods of Barcellos et al in view of Midgard et al would be obvious as applicable to at least the populations of Barcellos et al in view of Midgard et al, and that Applicants have provided no rationale as to why the evidence of the cited references is any less enabling than the evidence of the instant specification.

The rejection as set forth is **MAINTAINED**.

Conclusion

6. No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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